CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-141 and 21-176

MEDICAL REVIEW(S)

NDA 21-141/21-176
Welchol (colesevalam hydrochloride) capsules and tablets
Geltex Pharmaceuticals
Drug category: non-absorbed bile acid sequestrant
Indication: for the reduction of LDL-C in patients with primary hypercholesterolemia, either alone or in combination with an HMG-CoA reductase inhibitor
Date of submission: July 30, 1999
Date of review: May 9, 2000

Medical Team Leader comments on original NDA

Background
Colesevalam (CSV) is a new molecular entity. It is a non-absorbed bile acid sequestrant (BAS) indicated for cholesterol lowering. The safety and effectiveness of this mechanistic approach to the treatment of hypercholesterolemia has been established in clinical trials of other marketed BAS products. One in particular, cholestyramine, was studied in a large, multi-center, long-term, placebo-controlled outcome study, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT, LRC Trial), the results of which were published in the mid-1980's and submitted to the Agency for review. This study, which showed a significant reduction in the combined incidence of non-fatal MI and CHD death in the active treatment group, was seminal in establishing the rationale for the treatment of patients with elevated total and LDL-C in order to reduce the risk of adverse cardiovascular sequelae. Another landmark trial of cholestyramine, the NHLBI Type II Trial, also placebo controlled, was a 5-year study in a relatively small population that examined the effects of treatment on angiographic progression of atherosclerosis. Like LRC, this trial showed a statistical benefit associated with cholesterol lowering using cholestyramine.

Bile acid sequestrants deplete hepatic cholesterol pools (cholesterol is the precursor for bile acids) and induce a compensatory increase in the expression of LDL-receptors on hepatocytes. This effects an increased clearance of LDL particles from the plasma and lowers steady state LDL-C levels.

BAS drugs effect relatively modest reductions in total and LDL-C, particularly in comparison to currently marketed doses of some of the statins. Notwithstanding this, in the LRC study, a mean 10% reduction in LDL-C relative to baseline and placebo in the cholestyramine group was associated with a nearly 20% reduction in heart disease events. This finding provides, in part, the rationale for the established minimum efficacy criterion (mean 15% LDL-C reduction from baseline compared to placebo) for approval of an absorbed cholesterol lowering agent (DMEDP Guidelines, draft 1990). Based on the LRC results, our guidelines allow for lesser degrees of efficacy for non-absorbed drugs, based on the realization that they must be titrated to effect and also that they are most likely to be safer than systemically absorbed drugs, if not necessarily well tolerated.

The limitations to the use of BAS drugs have, with other products, resided largely in the GI side effects that accompany the large doses necessary to bind intestinal bile acids to a clinically significant degree. These side effects include bloating, cramping, constipation, and the like. In part because of poor tolerability, BAS drugs are not a frequent choice as first line therapy and are not frequently prescribed as monotherapy as the very high doses needed for substantial cholesterol lowering make compliance a major problem. Indeed therefore, much of the use of BAS is in relatively low daily doses in combination with other cholesterol lowering drugs, including statins and niacin, with which they have additive effects on LDL-C lowering. Of note, BAS drugs can induce hypertriglyceridemia and therefore are not recommended in patients with elevated TG at baseline. This effect is due to the compensatory increase in cholesterol biosynthesis in the liver and incorporation of some of that cholesterol into TG-rich lipoproteins secreted into the plasma.

BAS drugs have also been implicated in the impaired absorption of fat-soluble vitamins and some other drugs, including warfarin, thyroid hormone, thiazide diuretics, digoxin, propranolol, and furosemide. They have also been reported to lower levels of fat-soluble vitamins and folate after long-term use. Recommendations in the labeling for cholestyramine and colestipol are that they should be dosed apart from absorbed drugs so as not to adversely impact the therapeutic effects of these other agents.

Colesevalam is, like the other BAS products, an anion exchange resin, a positively charged polymer that binds avidly to negatively charged bile acids. It apparently has a significantly greater binding capacity than do the other products per weight of drug, and thus might be expected to be better tolerated for any degree of cholesterol lowering.

The sponsor has completed a comprehensive development program, investigating the safety and effectiveness of CSV both alone and in combination with three marketed statins in a series of double-blind, randomized, placebo-controlled trials. The safety exposures summarized in this NDA are substantial and the drug has been well-characterized with regard to tolerability and clinical and laboratory adverse events.

The materials reviewed for this note include volume 1.1 of the NDA which includes the application summary and the medical officer review by Dr. Shen dated 4-24-00.

Data summary

Clinical trials database

There were five Phase 2, two Phase 3, and one extended use study. All but the open-label extension study were randomized, double-blind, placebo-controlled trials. Study durations were from 4 weeks to 50 weeks. The highest dose studied was 4.5 gms daily in a large, 6-month, dose-ranging study (~100 patients per treatment group). At that dose, CSV treatment induced a mean 18% reduction in LDL-C from baseline. These data are summarized in labeling.

Combination treatment with low doses of three different HMGRIs (lovastatin, simvastatin, atorvastatin) produced additive effects on LDL-C lowering. These data are also summarized in labeling.

The effectiveness of CSV at the doses studied as monotherapy and as combination therapy supports the proposed indications for use to lower LDL-C in patients with primary hypercholesterolemia.

Exposures
Of 1374 patients treated in the Phase 2 and 3 clinical trials, 976 received CSV either alone or in combination with an HMGRI. 952 CSV-treated patients were included in the integrated analysis of safety. Average duration of exposure was 89 days for the CSV-only groups and 34 days for the CSV/HMGRI combination groups. Average durations of exposure across the CSV dose groups (low, medium, high) were 33, 103, and 96 days, respectively.

Adverse events
Gastrointestinal
The comparison of frequent (>5%) treatment emergent adverse events between placebo and CSV groups shows that CSV use was associated with higher incidences of the GI events of constipation (11% vs. 7%) and dyspepsia (8.3% vs. 3.5%). Consistent with the former effect of CSV, the incidence of diarrhea was higher in the placebo group. The incidence of constipation increased with increasing doses of CSV. Digestive system adverse events were, overall, the most common. The sponsor also compares the incidence of constipation and dyspepsia observed in the CSV trials to the historical data with cholestyramine. The latter has been associated with these GI adverse events in 20-30% of patients, as compared to between 5 and 15% for CSV. Of note, no head-to-head clinical comparisons of CSV and the older BAS were conducted as part of this NDA.

Liver function testing
Minor elevations in hepatic transaminases were observed in a few CSV-treated patients, a phenomenon observed with other members of this drug class due to increased metabolic activity of the liver as bile acid synthesis and secretion are upregulated in response to intestinal bile acid sequestration and hepatic cholesterol depletion.

Fat-soluble vitamins
The effects on fat soluble vitamins, including vitamins A, E, and K were monitored in the CSV clinical trials. There was no evidence of an effect of CSV to deplete fat-soluble vitamins though exposures were of limited duration (up to 1 year). There was no evidence of an effect of CSV treatment on INR, the measure of vitamin K status.

Drug-drug interactions
With regard to drug-drug interactions with CSV, the sponsor conducted a series of studies to examine the effects on the pharmacokinetics of the absorbed drug of coadministration of CSV. Drugs included lovastatin, quinidine, valproic acid, digoxin, warfarin,

verapamil, and metoprolol. The only remarkable result was in the combination study with verapamil. Coadministration of CSV and verapamil resulted in a blunting of the peak plasma levels of verapamil and its metabolite, though the sponsor points out that the extent of blunting does not exceed the variability known to characterize the pharmacokinetics of verapamil, a drug that is thus used in a titrate-to-effect manner. In sum, then, there were no clinically important interactions between CSV and the drugs studied.

Tolerability of CSV tablets

Two NDA's were submitted for CSV: one for tablets and one for capsules. The clinical trials were all conducted with capsules and the sponsor proposes ——— A bridging tolerability study was conducted in 20 male and female normal volunteers who took CSV tablets (6/day) for 4 weeks and were interviewed to assess tolerability with particular regard to swallowing. No patient complained of gagging or choking.

Labeling

The original proposed labeling for CSV was deficient with regard to format and contained substantial information that constituted implied claims of comparative (superior) efficacy and safety to marketed BAS products. In addition, reference was made in Clinical Pharmacology to the ——— also effecting an implied claim of ——— These problems have all been rectified after discussion with the Division.

The current proposed labeling contains tabular summaries of efficacy data for CSV alone and in combination with HMGRIs. Tabular summary of safety data compares placebo to CSV-alone patients. CSV is indicated for use as monotherapy or in combination with an HMGRI in patients with primary hypercholesterolemia. CSV is contraindicated in individuals with bowel obstruction and should be used with caution in patients with TG levels greater than 300 mg/dL as well as in patients with a susceptibility to fat-soluble vitamin deficiencies. Because of the relative paucity of data on interactions with other drugs, the label contains the following cautionary statement: "When administering other drugs for which alterations in blood levels could have a clinically significant effect on safety and efficacy, physicians should consider monitoring drug levels or effects."

The Pregnancy Category is B (studies in two animal species have revealed no evidence of impaired fertility or harm to the fetus).

The sponsor has submitted proposed labeling for both tablets and capsules.

Drug name

The original proposed name was Cholestagel. Tradename review found this unacceptable, and the sponsor proposed the name Welchol. OPDRA review pointed to possible confusion with Medrol and recommended against the name. The sponsor subsequently submitted the findings of a drug name effectiveness study. This study found no evidence to suggest a potential for confusion with Medrol. The Medical Team

has concluded the following: Medrol is most frequently prescribed as "Dose-pack," and thus dispensed for relative short-term use. Medrol tablets are small (4mg) as compared to Welchol (625 mg). Welchol will be prescribed for use one or two times per day with meals for chronic use. The possibility of confusion between Welchol and Medrol seems remote.

Financial disclosure
Form OMB No. 0910-0396 was included in the submission and signed by the CFO of Geltex. This form certifies that the sponsor has not entered into any financial arrangement with the clinical investigators listed by study in the pages following the form. Thus, there is no evidence that any of the investigators had a financial interest in the outcomes of the studies.

Summary and conclusions
This NDA contains data from adequate and well-controlled trials to support the effectiveness and safety of CSV, either alone or in combination with an HMGRI, at the doses recommended and according to the directions for use described in labeling for the treatment of patients with primary hypercholesterolemia. The current proposed labeling is accepted. The proposed name, Welchol, is accepted.

Recommendations
This NDA should be approved.

David G. Orloff, M.D.
Deputy Director/ Medical Team Ldr
DMEDP/CDER/FDA

Recommendation code: AP

/S/ 5-8-00

CC:
NDA 21-141 Arch
NDA 21-176 Arch
HFD-510

APPEARS THIS WAY
ON ORIGINAL

NDA 21-141/21-176
Welchol (colesevalam hydrochloride) capsules and tablets
Geltex Pharmaceuticals
Drug category: non-absorbed bile acid sequestrant
Indication: for the reduction of LDL-C in patients with primary hypercholesterolemia, either alone or in combination with an HMG-CoA reductase inhibitor
Date of submission: July 30, 1999
Date of review: May 16, 2000

Addendum to Medical Team Leader comments on original NDA: review of financial disclosure information submitted to NDAs

The following financial disclosure information has been submitted:

1. Form OMB No. 0910-0396. The sponsor certifies that Geltex has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study (outcome payments). The sponsor further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in the company. Finally the sponsor certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment.
2. List of investigators from whom completed financial disclosure forms were received.
3. Certification pursuant to 21 CFR 54.5(c) that the sponsor acted with due diligence to obtain financial disclosure information from a list of – investigators from whom completed forms were never received.
4. List of – investigators not submitting financial disclosure information and the studies to which they contributed data.

Comments

The investigators listed as not submitting financial disclosure forms each contributed data from single sites in large, multicenter trials. Analyses of efficacy data in this NDA did not reveal any significant effect of center on outcomes. Furthermore, the data on both safety and effectiveness were consistent across the multiple trials submitted to the NDA. In sum, the absence of financial disclosure information from the – investigators listed does not call into question the overall integrity of the data submitted.

David G. Orloff, M.D.
Deputy Director/Med Tm Ldr
DMEDP/CDER/FDA

/S/ 5-16-00

CC:
NDA Arch 21-141/21-176
HFD 510

NDA: 21-141 (capsules) /21-176 (tablets).

Drug: Colesevelam hydrochloride.

Sponsor: GelTex Pharmaceuticals, Inc.
Pharmacologic Category: Bile-Acid Sequestrants. .
Route of Administration: Oral.
Proposed Indication: Alone or in combination with HMG-CoA reductase inhibitor, as adjunctive therapy to diet and exercise for the reduction of elevated LDL - C in patients with primary hypercholesterolemia.
Proposed Dosage(s): — 4.5 g/day.
Date Submitted: 7/30/99
Date Review Completed:

Preliminary Version : 4/10/00
Final Version: 4/19/00-4/24/00

TABLE OF CONTENTS:

List of Abbreviations used in this review:

ATO: Atorvastatin
CSV: Colesevelam
GI: :Gastrointestinal
LOV: Lovastatin
Med. Hx: medical history
Pre-meno/post w/hormone: Pre&post menopausal females with hormone supplement.
Post w/o hormone: post menopausal females without hormone supplement.
SIM :Simvastatin
ULN: upper limit of normal
Vit: Vitamin.

APPEARS THIS WAY
ON ORIGINAL

Administrative Background:

The submission for Colesevelam HCL had been designated with two NDA numbers: 21-141/N-000 for the 375 mg capsule, and 21-176/N-000 for the 625 mg tablet. [redacted]. All data had been submitted to NDA 21-141/N-000 but all memos/reviews will cross-reference 21-176/N-000 for completeness.

Trade name review found the name "Cholestagel" unacceptable, the sponsor proposed the name "Welchol" in the 2/3/00 Amendment. Trade name review is pending.

Clinical Background:

Historical Perspectives of Bile Acid Sequestrants:

Bile acid sequestrants were among the first drugs approved for lowering cholesterol. Bile acid sequestrants are generally non-absorbed and complex with bile acids in the intestine, decreasing their absorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7–hydroxylase is upregulated, increasing the conversion of cholesterol to bile acids. Increased cholesterol degradation causes an increase in cholesterol biosynthesis and an increase in LDL cholesterol receptor expression. This results in lowering LDL cholesterol by increasing the clearance of LDL cholesterol and VLDL remnants from the circulation. The increased VLDL production may increase TG during therapy with bile acid sequestrants. Therefore, bile acid sequestrants are not used as monotherapy in patients with II-B or mixed hyperlipidemia.

The two most widely used bile acid sequestrants are cholestyramine and colestipol. At full dosage, 10-20% lowering of LDL-C may be achieved. However, at these large daily doses, there is high incidence of GI side-effects, particularly constipation and flatulence resulting in a 41 to 63% annual discontinuation rate. Furthermore, there are drug-drug interactions with many other drugs, altering the pharmacokinetics of warfarin, phenylbutazone, penicillin G, thyroid hormone, thiazide diuretics, amiodarone, cardiac glycosides, phenobarbitol, propranolol, tetracycline, furosemide, gemfibrozil, and digitoxin. Finally, bile acid sequestrants have been reported to lower fat-soluble vitamins and folate after prolonged use. Clinically, this is of particular concern in children and in pregnant women.

Colesevelam HCL is a cross-linked polymer; each particle is one molecule due to multiple covalent cross-links between polymer chains. Bile acid binding per gram of colesevelam HCL is about 3-4 fold more than older BAS agents (cholestyramine and colestipol). This review will therefore focus on the efficacy (as monotherapy and in combination with statins) and possible safety concerns of adverse effects on fat-soluble vitamins.

Chemistry/Manufacturing Controls:

The chemical name is 1-Hevanamminium, N.N.N-trimehtyl-6-(2-propenylamine)-,chloride, polymer with (chloromethyl)oxirane,2-propen-1-amine and N-2-propenyl-1-decanamine, hydrochloride. For structural formula and other details, please see Chemistry Review.

Preclinical Pharmacology/Toxicology:

Please see Pharmacology Review.

Human Pharmacology/Pharmacokinetics:

Please see Biopharmacology Review.

Description of Clinical Data Sources:

1. Protocol GTC-37-201 was designed to determine the safety and efficacy of colesevelam HCL at 4 doses ranging from 1.5 g to 3.8 g per day. About ~30 patients per arm.
2. Protocol GTC-37-202 was designed to determine the efficacy of alternative dosing schedules, once a day in a.m. or p.m. and split daily dosing with breakfast and dinner. The study dose was 1.5 g and ~30 patients per arm.
3. Protocol GTC-48-301 was a pivotal Phase 3 dose-ranging study designed to determine the long-term (6 months) safety and efficacy. There were 5 arms (placebo, 2.3, 3.0 3.8 and 4.5 g) with ~90 patients in each arm.
4. Protocol GTC-37-901 was a dose titration extension study of Protocol GTC-48-301 designed to evaluate the safety and efficacy over 1 year. 186 patients completed the study at 50 weeks.
5. Protocol GTC-48-302 was a pivotal Phase 3 study designed in a similar manner as GTC-37-202 to confirm the efficacy of once a day and split daily doses. 90 patients completed this 6-week study.
6. Protocols GTC-37-203, GTC-37-48-204 and GTC-48-205 were designed to determine the safety and efficacy of colesevelam HCL in combination with statins: lovastatin, simvastatin and atorvastatin respectively.
7. Protocol GTC-44-201, the only study with colesevelam HCL tablet, was designed to test the tolerability of a tablet formulation in normal healthy volunteers. 18 subjects completed the study.

Review of Individual Clinical Studies:

The principal clinical studies were Protocol GTC-48-301, a pivotal Phase 3 dose-ranging study designed to determine the long-term safety and efficacy of colesevelam HCL in patients with primary hypercholesterolemia and Protocol GTC-48-302, a pivotal Phase 3 study designed to confirm the efficacy of once a day and split daily doses .

Table 1. Table of Pivotal Phase 3 Clinical Studies:

Study	N	Treatment	Treatment Duration
Protocol GTC-48-301	467	Placebo; Colesevelam 2.3, 3.0, 3.8 and 4.8 g/day	6 months
Protocol GTC-48-302	94	Placebo; Colesevelam 3.8 g AM, 3.8 g PM, 1.9 g BID	6 weeks

Protocol GTC-48-301: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-design study.

I. Objectives:

The primary objectives of this study were to determine the safety of Colesevelam HCL and the efficacy in reducing serum LDL-C levels in patients with primary hypercholesterolemia during a 6-month treatment period.

The secondary objectives of this study were to demonstrate the efficacy of Colesevelam HCL on TC, TG, HDL-C, lipoprotein, and apolipoproteins in patients with primary hypercholesterolemia during a 6-month treatment period.

A. Patient Selection:

1. Inclusion Criteria:

1). Men or women 18 years of age or older;
2). LDL cholesterol level at Visit 2 >130 mg/dL and < 220 mg/dL and a triglyceride level <300 mg/dL;
3). Willing to adhere to the NCEP Step 1 diet program during the study;
4). Willing to avoid intentional changes in diet during the study, such as fasting or binge eating;
5). Ate, on most days, at least two meals per day, one of which was breakfast or lunch and the other dinner;
6). If taking a fiber supplement (cellulose, methylcellulose, psyllium, polycarbophil, or bran) were willing to maintain a constant dose throughout the study;
7). If taking androgen, estrogen, progesterone, oral steroid, thiazide diuretic, or beta-blocker, the prescribed dose must have been stable for 30 days prior to screening. Cyclic administration of estrogen and progesterone were acceptable in pre-menopausal women;
8). If a woman of child-bearing potential, had negative pregnancy test at screening and prior to randomization;
9). If a woman of child-bearing potential (pre-menopausal and not surgically sterilized), had an intrauterine device (IUD) or used hormonal, or barrier

(condom or diaphragm and spermicide) methods of contraception for the duration of the study;

2. **Exclusion Criteria:**

1). Untreated thyroid disease, clinically significant liver or renal disease, vasculitis, HIV infection, poorly controlled diabetes mellitus (FBS >200 mg/dL), poorly controlled hypertension (systolic BP >160 mm Hg or diastolic BP >105 mm Hg), unstable cardiac disease, recent myocardial infarction or cardiac bypass surgery/PTCA (within 2 months of screening), or any clinically significant unstable medical condition (as defined by the investigator);
2). A history of dysphagia or swallowing disorders or motility disorder of the intestines, including but not limited to gastroparesis, ileus, pseudo-obstruction, megacolon, or mechanical obstruction;
3). Participated in a study of an investigational drug during the 30 days preceding the start of the Screening period;
4). Used lipid lowering medication during the study;
5). Used probucol in the year prior to Screening or had used fibrates in the month prior to Screening;
6). Had active ethanol or drug dependence or abuse, excluding tobacco use;
7). Were breast-feeding;
8). Had the following laboratory abnormalities on the screening blood tests: hemoglobin <11.0 g/dL, ALT >upper limit of normal (ULN);
9). Had previous exposure to Colesevelam;
10). Has any evidence of active malignancy, except for basal cell carcinoma of the skin. History of a malignancy was not an exclusion.

II. Study Design and Procedures:

Following screening, 962 patients with primary hypercholesterolemia entered the diet period. After a minimum 8 weeks diet period patients meeting the entrance criteria were enrolled into one the following dosage groups:

1. Total daily dose Colesevelam 2.3 g: 3 capsules of Colesevelam plus 3 capsules of placebo, BID.
2. Total daily dose Colesevelam 3.0 g: 4 capsules of Colesevelam plus 2 capsules of placebo, BID.
3. Total daily dose of Colesevelam 3.8 g: 5 capsules of Colesevelam plus 1 capsule of placebo, BID.
4. Total daily dose of Colesevelam 4.5 g: 6 capsules of Colesevelam BID.
5. Placebo: 6 capsules of placebo, BID. (Composition: — % microcrystalline cellulose and —% magnesium stearate.)

The study was divided into the following periods:

Screening Period (Visit 1):

Diet Period (Visits 2-4): Lasted a minimum of 8 weeks and patients were placed on NCEP Step 1 diet.

Baseline Period (Visits 3-4): Fasting lipid profile, chemistry, CBC, PT, PTT, and vitamins A and E) were obtained. Patients were randomized at Visit 4 and instructed to begin taking the study medication that day.

Treatment Period (Visits 5-11): Visit 5 occurred 2 weeks after Visit 4 and Visit 6 occurred 2 weeks later. Then monthly visits were arranged for Visits 7-11.

The detailed study procedures are shown below:

Table II-1: Flow Chart

	Screening	Diet	Baseline		Treatment						
Visit # Days	1	2-4 -28±3	3 7±3	4 Day 0	5 14±3	6 28±3	7 56±3	8 84±3	9 112±	10 140±3	11 168±3
Med./Meds Hx.	*										
PE/.vital signs		*									*
Chem. Profile, CBC	*			*				*			*
PT,PTT, vit. A&E				*				*			*
Serum HCG	*		*								
Fasting lipid profile	*	*	*	*	*	*	*	*	*	*	*
TSH/T4	*										
Diet info.	*	*	*	*	*	*	*	*	*	*	
Dispense drugs				*		*	*	*	*	*	
Adverse events		*	*	*	*	*	*	*	*	*	*
Drugs counting						*	*	*	*	*	*

II. A. Patient Characteristics:

The ITT population included those patients who had at least one valid (12-hour fasting state and medication taken within 48 hours) post -baseline lipid evaluation}.

The Evaluable population was defined as those patients who completed the study at Day 168, and were at least 80% compliant with the study medication.

Table II-2. Patient Demographics at Baseline, Intent-to-Treat Population:

	Placebo	CSV 2.3 g	CSV 3.0 g	CSV 3.8 g	CSV 4.5 g	Total
Variable	N=88	N=99	N=91	N=95	N=94	N=467
Age (years)						
Mean	55.0	56.6	56.7	56.3	52.9	55.5
<65 N (%)	65 (73.9)	66 (66.7)	71 (78.0)	68 (71.6)	77 (81.9)	347 (74.3)
>65 N (%)	23 (26.1)	33 (33.3)	20 (22.0)	27 (28.4)	17 (18.1)	120 (25.7)
Gender						
Male N (%)	42 (47.7)	50 (50.5)	47 (51.6)	45 (47.4)	48 (51.1)	232 (49.7)
Female N (%)	46 (52.3)	49 (49.5)	44 (48.4)	50 (52.6)	46 (48.9)	235 (50.3)
Female Menopausal & Hormone Supplement Status						
Pre-meno/ post w/ hormone N (%)	30 (65.2)	25 (51.0)	23 (52.3)	27 (54.0)	29 (63.0)	134 (57.0)
Post w/o Hormone N (%)	16 (34.8)	24 (49,0)	21 (47.7)	23 (46.0)	17 (37.0)	101 (43.0)
Weight (kg)						
N	88	99	90	95	93	465
Mean	79.3	81.1	87.1	86.1	85.8	83.9
Body Mass Index (kg/m2)						
N	88	99	90	95	92	464
Mean	27.9	28.3	29.7	30.2	30.0	29.3
Baseline LDL-C (mg/dL)						
<160 N (%)	53 (60.2)	49 (49.5)	52 (57.1)	58 (61.1)	55 (58.5)	267 (57.2)
160-190 N (%)	31 (35.2)	46 (46.5)	28 (30.8)	30 (31.6)	37 (39.4)	172 (36.8)
>190 N (%)	4 (4.5)	4 (4.0)	10 (11.0)	7 (7.4)	2 (2.1)	27 (5.8)

CSV=Colesevelam. This abbreviation will be used throughout this review..
Pre-meno/post w/hormone=pre-& post menopausal females with hormone supplement.
Post w/o hormone=post menopausal females without hormone supplement.

The treatment groups were similar with respect to most of the demographic characteristics. The sponsor performed ANOVA for continuous variables and Chi Square test for categorical variables. For the most parts, there were no significant differences across the treatment groups. The only exceptions were for weight (p-

value= 0.0120) and body mass index (p-value= 0.01150). However, the actual differences in weight and body mass index were small and unlikely to affect the results of the study.

About 2% of the ITT patients in each treatment group were excluded as shown, the colesevelam-treated groups did not have more patients excluded.

Reason for Exclusion						
	Placebo	CSV 2.3 g	CSV 3.0 g	CSV 3.8 g	CSV 4.5 g	Total
Didn't complete Day 168	14	19	15	19	18	85
<80% complian.	3	6	7	6	7	29
Evaluable	71	74	69	70	69	353

II B. Patient Accounting: Of the 494 patients randomized, a total of 382 patients completed the study. Reasons for premature discontinuation are shown in the table below:

Table II-3: Reasons for Patient Discontinuation.

Reasons Discontinua -tion	Total N=494 N%	Placebo N=94 N%	CSV2.3 g N=94 N%	CSV 3.0 g N=98 N%	CSV 3.8 g N=101 N%	CSV 4.5 g N=99 N%
Adverse Event	49 (9.9)	6(6.4)	14(13.7)	11(11.2)	9(8.9)	9(9.1)
Protocol Violation	5(1.0)	1(1.1)	1(1.0)	3(3.1)	0(0.0)	0(0.0)
Consent withdrawn	42(8.5)	10(10.6)	7(6.9)	4(4.1)	11(10.9)	10(10.1)
Lost to F/U	12 (2.4)	3(3.2)	0(0.0)	3(3.1)	4(4.0)	2(2.0)
Other	4(0.8)	0(0.0)	0(0.0)	1(1.0)	1(1.0)	2(2.0)

49 patients (9.9%) prematurely discontinued from the study due to adverse events as listed above. The colesevelam-treated groups had higher percentage of adverse events. The GI adverse events were most common. Other adverse events included hypothyroidism (placebo-treated), twitching, urinary frequency, back pain, arrhythmia, chills and vomiting. There was no increased frequency of the other reasons for discontinuation in the colesevelam-treated groups.

III. Results:

A. Safety:

1. Death: There were no deaths in this study.

2. Serious Clinical Adverse Events: 12 patients were hospitalized for the serious adverse events during the study and none of these were related to the study drug:

a). Placebo Group: One patient for back and shoulder pain.
One patient for skin biopsy.
One for URI with pleurisy.

b). 2.3 g Group: One patient for "passed out".
Two patients for severe chest pain.

c). 3.0 g Group: One patient for atrial fibrillation.
One patient for hematoma resulting from trauma.

d). 3.8 g Group: One patient for chest pain.
One patient for elective surgery for nerve impingement.
One patient for elective cholecystectomy.
One patient for knee replacement.

3. Laboratory Adverse Events: There were no statistically significant changes in chemistry parameters and no patient had a clinically significant chemistry abnormality. Other treatment-related abnormalities are shown below:

a. There was a small but statistically significant decrease in mean glucose levels in the active-treatment groups:

Table III-1: Mean change in fasting glucose Day 0 to Day 168:

				Change	
Parameter/ Treatment	N	Day 0	Day 168	Mean	p-value*
Glucose (mg/dL)					
Placebo	87	96.01	98.47	+2.46	0.3542
CSV 2.3 g	99	96.12	95.62	-0.51	0.1604
CSV 3.0 g	88	97.43	97.27	-0.16	0.7779
CSV 3.8 g	93	101.19	98.43	-2.76	0.0044
CSV 4.5 g	87	95.48	93.32	-2.16	0.0081

- P-value based on paired t-test from Day 0 to Day 168.

The greatest decrease occurred in the 3.8 g group. In this group, the range of glucose concentration was from — mg /dL to — mg/dL. There were 4 patients with blood glucose < 55-60 mg/dL in this study; none of them was symptomatic. Since 3 of the patients were in the placebo-group, it is unlikely that the one patient in the 4.5 g-group was due to colesevelam treatment.

b. Liver function tests: There was no statistically significant change in mean SGOT levels between the placebo-treated and the colsevelam -treated groups. There were minor although statistically significant increases in mean ALT(SGPT) and Alkaline Phosphatase as shown below:

Table III-2: Mean change in ALT(SGPT) & Alkaline Phosphatase Day 0 to Day 168:

Parameter/ Treatment	N	Day 0	Day 168	Change	
ALT (SGPT) mU/mL				**Mean**	**P-value***
Placebo	87	14.31	15.47	1.16	0.2032
CSV 2.3 g	99	14.57	15.01	0.44	0.0813
CSV 3.0 g	88	14.43	16.24	1.81	0.0010
CSV 3.8 g	94	15.05	17.71	2.66	0.0002
CSV 4.5 g	87	15.08	17.10	2.02	0.0015
ALK. Phos (mU/mL)					
Placebo	87	51.71	53.24	1.53	0.0281
CSV 2.3 g	99	52.07	54.60	2.53	0.0003
CSV 3.0 g	88	53.49	56.89	3.40	<0.0001
CSV 3.8 g	94	53.74	59.18	5.44	<0.0001
CSV 4.5 g	87	53.00	56.86	3.86	<0.0001

* P-value based on paired t-test from Day 0 to Day 168.

Comments: Compared to Day 0, there were statistically significant mean elevations of SGPT and Alkaline Phosphatase as shown. These small mean elevations of SGPT and Alkaline Phosphatase were <3xULN.) There was no patient with >3xULN elevation of Alkaline Phosphatase. However there was one patient each with high SGOT and SGPT respectively:

(1). Patient 301.001.011 in the 3.8 g group: This 61-year-old female patient had SGOT of 27 mU/mL on the Screen Visit (normal range: 8.0-22.0), increased to 34 on Day 0 of treatment, to 54 on Day 85, to 77 on Day 170 and decreased to 47 on Day 184 of treatment. This patient also had elevated SGPT(ALT) of 29 (Normal range 5.0-25.0 mU/mL) on Screen, increased to 54/ 63 on Days 85/170 of treatment and decreased to 44 of Day 184 of treatment. Patient was clinically asymptomatic and the bilirubin was not increased.

(2). Patient 301.008.004 in the 2.3 g group: This 39 year-old male patient had SGPT of 29 (normal range 5.0-25.0 mU/mL) on Screen, increased to 76/41 on Days 90/97 of treatment and decreased to 39 on 175 Day of treatment. This patient was asymptomatic and bilirubin was not increased.

C. Changes in fat-soluble vitamins: vitamin K, A, and E.

1. Vitamin K: In Vitamin K deficiency, all vitamin K-dependent plasma glycoproteins, Factors II, VII, IX and X are depressed. Clinical significant vitamin K deficiency prolongs the prothrombin time (PT) due to depression of Factor VII. PTT will be normal initially and then become prolonged as Factors IX and X fall more slowly.

(a). There were statistically significant mean changes in PT. However, the mean values were <1.2XULN/<20 seconds. 3 patients had vakues >1.2XULN/>20 seconds:

(1). Patient 301.005.011 inn the 3.0 g group: This 63-year-old male had PT of 12.70 (normal range 10.5-13.5), increased to 23.00/24.70 on Days 127/212 of treatment. He also had high PTT values. The increased PT is most likely due to the fact that this patient was taking warfarin during the study. Colesevelam was found to have no significant effect on the bioavailability of warfarin. He did not develop clinical episodes of bleeding.

(2). Patient 301.006.035 in the 3.0 g group: This 51-year-old female had PT of 12.40, increased to 18.20 on Day 84 of treatment but decreased to 11.70 on Day 168 of treatment. She did not develop any clinical episode of bleeding.

(3). Patient 301.009.038 in the 3.8n g group: This 63-year-old male had PT of 11.80, increased to 16.50/14.70/16.80 on Days 116/141/169 of treatment. The increased in PT is most likely due to the fact that this patient was taking warfarin during the study. He did not develop clinical episodes of bleeding.

(b). There were statistically significant mean changes in PTT for patients in the colesevelam-treated groups except the 3.0 g-group. However, the mean values were <1.2XULN/<35 seconds. 4 patients (in addition to Patient 301.005.001 described above) had values >1.2XULN/>35 seconds:

(1). Patient 301.005.018 in the 3.0 g group : This 59-year-old male had PTT of 22.30 (Normal range 21.0-31.0), increased to 37.10 on Day 182 of treatment. He did not develop clinical episodes of bleeding.

(2). Patient 301.005.007 in 3.8 g group: This 59-year-old male had PTT of 25.80, increased to 32.5/37.50 on Days 180/196. He did not develop clinical episodes of bleeding.

(3). Patient 301.005.034 in the 4.5 g group: This 42-year-old female had PTT of 30.60, increased to 37.60 on Day 176 of treatment. She did not develop clinical episode of bleeding.

(4). Patient 301.017.004 in the 4.5 g group: This 66-year-old male had PTT of 23, 30, increased to 36.40 on Day 170 of treatment but decreased to 21.0, 12 days later. No clinical episode of bleeding occurred.

2. There were statistically significant mean changes in Vitamin A in both placebo and all CSV-treatment groups. The absolute magnitude of the changes was similar or slightly greater for the CSV-treatment groups than for the placebo group.
3. The vitamin E group includes the alpha, beta, gamma, and delta tocopherols; alpha is the most active. There were statistically significant changes in alpha tocopherol in both placebo and all CSV-treatment groups.

The absolute magnitude of the changes was similar or slightly greater for the CSV-treatment groups than for the placebo group. No patient developed clinical evidence of alpha-tocopherol deficiency. Tocopherols act as antioxidants to prevent lipid peroxidation of polyunsaturated fatty acids in cells and maintain membrane integrity. Deficiency in man causes RBC hemolysis, creatinuria, and deposit of ceroid (lipid pigment) in muscle and in CNS. Neurologic changes consisting of cerebellar ataxia, posterior column dysfunction and peripheral neuropathy.

4. There were no statistically significant mean changes in gamma tocopherol in the CSV-treatment groups compared to placebo group. However, there were 6 patients with low gamma tocopherol levels:
   a. Colesevelam 2.3 g:
      (1). Patient 301.006.009: This 51-year-old male had gamma tocopherol of 0.03 (normal range 0.05-0.30 mg/dL), decreased to 0.02 on Day 171 of treatment.
      (2). Patient301.017.022: This 48-year-old male had gamma tocopherol of 0.05, decreased to 0.02 on Day 168 of treatment.
   b. Colesevelam 3.0 g:
      (1). Patient 301.003.006: This 53-year-old female had gamma tocopherol of 0.06, decreased to 0.02 on Day 124 of treatment.
      (2). Patient 301.010.033: This 64-year-old male had gamma tocopherol of 0.07, decreased to 0.02 on Day 84 but increased to 0.08 on Day 168 of treatment.
   c. Colesevelam 4.5 g:
      (1). Patient 301.006.037: This 57-year-old male had gamma tocopherol of 0.03, decreased to 0.02/0.03/0.04 on Days 18/84/168 of treatment.
      (2). Patient301.014.026: This 70-year-old female had gamma tocopherol of 0.04, decreased to 0.02 of Day 166 of treatment.

The decrease in gamma tocopherol was not dose-dependent and none of the patients manifested any clinical signs/symptoms of deficiency.

B. Efficacy:

1. **Primary Efficacy:** The primary efficacy endpoint was the mean change in LDL-C from baseline to the end of the treatment period. These changes are shown in Tables III-3, III-4 :

Table III-3: Mean and Median Change in LDL-Cholesterol from Baseline to Endpoint—ITT Population:

Treatment Group	N	Baseline (mg/dL)		Endpoint (mg/dL)		Percent Change		
		Mean	Median	Mean	Median	Mean	Median	P-value*
Placebo	88	155.1	152.3	154.8	155.3	0.4	0.8	0.7905
CSV 2.3 g	99	160.6	160.0	146.5	145.5	-08.6	-09.3	<0.0001
CSV 3.0 g	90	160.4	155.8	141.1	139.3	-11.7	-12.4	<0.0001
CSV 3.8 g	95	158.6	154.0	134.6	134.0	-14.6	-16.3	<0.0001
CSV 4.5 g	94	155.5	156.8	127.4	124.8	-18.0	-19.6	<0.0001

* P-value based on paired t-test from baseline to endpoint.

Table III-4: Mean Percent Change in LDL-C from Baseline to Endpoint Subgroups Stratified by Baseline LDL-C Level—ITT Population:

Subgroup /Treatment	N	Baseline (mg/dL)	Endpoint (mg/dL)	Percent Change	
				Mean	P-value**
LDL-C≤160 mg/dL					
Placebo	53	142.5	146.7	3.2	0.0207
CSV 2.3 g	49	146.2	135.5	-7.3	0.0001
CSV 3.0 g	52	144.9	130.2	-10.0	<0.0001
CSV 3.8 g	58	144.6	126.1	-12.6	<0.0001
CSV 4.5 g	55	143.7	117.2	-18.4	<0.0001
LDL-C≥160 & ≤190 mg/dL					
Placebo	31	170.9	162.2	-4.8	0.0170
CSV 2.3 g	46	172.2	156.7	-9.2	<0.0001
CSV 3.0 g	28	172.2	147.9	-14.1	<0.0001
CSV 3.8 g	30	174.8	143.1	-17.5	<0.0001
CSV 4.5 g	37	170.9	140.8	-17.5	<0.0001
LDL-C≥190 mg/dL					
Placebo	4	199.0	202.4	1.9	1.0000
CSV 2.3 g	4	202.8	163.8	-19.1	0.1250
CSV 3.0 g	10	207.4	178.5	-14.3	0.0039
CSV 3.8 g	7	204.9	169.4	-17.5	0.0156
CSV 4.5 g	2	195.3	160.0	-18.0	0.5000

** P-value based on Wilcoxon Signed-Rank test from baseline to endpoint.

Comments:

1). The mean and median LDL-C levels at endpoint for all the colesevelam-treated groups were statistically significantly different from placebo group($p<0.0001$).

2). The more important parameter was the mean and median percent change from Baseline to Endpoint for each treatment group. According to the Agency Guideline, LDL-C reduction should be ≥ 15% for lipid-lowering drug approval. Only the Colesevelam groups treated with ≥ 3.8 g resulted in ≥ 15 % percent LDL-C reductions.

3). Across the strata of LDL-C levels of ≤160 mg/dL and LDL-C ≥160 and ≤190 mg/dL, there was no statistically significant difference in mean percent reduction in LDL-C. The patient population LDL-C≥ 190 mg/Dl subgroup had too few patients to warrant meaningful conclusions.

2. Secondary Efficacy:

a. Total Cholesterol: The mean change and percent change in total cholesterol is shown below:

Table III-5: Mean Change and Percent Change in Total Cholesterol from Baseline to Endpoint—ITT population:

Treatment Group	N	Baseline (mg/dL)	Endpoint (mg/dL)	Change (mg/dL)	P-value*	Percent Change	P-value*
Placebo	88	242.1	243.8	1.6	0.4296	0.0	0.3091
CSV 2.3 g	99	244.9	234.9	-10.0	<0.0001	-4.1	<0.0001
CSV 3.0 g	91	244.7	229.3	-15.4	<0.0001	-6.2	<0.0001
CSV 3.8 g	95	244.8	226.8	-18.0	<0.0001	-7.1	<0.0001
CSV 4.5 g	94	240.0	216.3	-23.6	<0.0001	-9.8	<0.0001

* P-value base on paired t-test from baseline to endpoint.

Comments:

1). The mean and median total-C levels at Endpoint for all the colesevelam-treated groups were statistically significantly different from placebo group ($p<0.0001$).

2). The more important parameter, the mean percent change in total-C from Baseline to Endpoint, in each Colesevelam treatment group was statistically different. However, unlike LDL-C, there is no established percent total-C reduction that is considered to be clinically significant.

b. HDL cholesterol: The median change and percent change in HDL cholesterol is shown below:

Table III-6: Median Change and Percent Change in HDL Cholesterol from Baseline to Endpoint—ITT population:

Treatment Group	N	Baseline (mg/dL)	Endpoint (mg/dL)	Change (mg/dL)	P-value*	Percent Change	P-value*
Placebo	88	50.0	52.0	-0.5	0.5378	-1.1	0.2681
CSV 2.3 g	99	50.0	51.5	1.5	0.0010	2.6	0.0003
CSV 3.0 g	91	48.5	51.5	2.0	0.0004	3.9	<0.0001
CSV 3.8 g	95	47.5	49.0	1.5	0.0003	2.9	0.0001
CSV 4.5 g	94	48.0	50.5	1.5	0.0006	2.6	0.0003

* P-value based on Wilcoxon Signed Rank test from baseline to endpoint.

c. TG: The median change and percent change in TG is shown below:

Table III-7: Median Change and Percent Change in TG from Baseline to Endpoint—ITT population:

Treatment Group	N	Baseline (mg/dL)	Endpoint (mg/dL)	Change (mg/dL)	P-value*	Percent Change	P-value*
Placebo	88	170.8	173.8	4.5	0.1691	4.6	0.0701
CSV 2.3 g	99	148.0	166.0	11.5	0.0120	8.6	0.0022
CSV 3.0 g	91	158.5	164.5	7.5	0.0635	4.8	0.0148
CSV 3.8 g	95	172.5	172.0	15.5	0.0003	9.9	<0.0001
CSV 4.5 g	94	156.0	165.3	10.8	0.0105	9.4	0.0017

* P-value base on Wilcoxon Signed Rank test from baseline to endpoint.

Comments:

1). Compared to the placebo-group, for both HDL-C and TG, the median percent changes were not statistically significant by Kruskal-Wallis test: for HDL-C (p-values = 0.1081) and for TG (p-value = 0.4234).

2). The percent changes for HDL-C from baseline to endpoint in CSV-treated groups were statistically significantly different. However, the cardiovascular significance of these degrees of increase is unknown.

3). The percent changes for TG from baseline to endpoint in CSV-treated groups were statistically significantly different. Again, the cardiovascular significance of these degrees of increases is unknown. Patients with TG >300 mg/dL were excluded from the study. No patient reached TG≥ 750 mg/dL at the Endpoint. One patient in the 3.8 g-group had TG of 722 mg/dL at one month and decreased to 114 mg/dL at Endpoint. One patient in the 4.5 g-group had TG of 576 mg/dL at one month and decreased to 417 mg/dL at endpoint.

d. Apolipoprotein B: Mean change and percent change are shown below:

Table III-8: Mean Change and Percent Change in Apolipoprotein B from Day 0 to Day 168/Early Termination—ITT Population:

Parameter /Treatment	N	Baseline (mg/dL)	Endpoint (mg/dL)	Change (mg/dL)	P-value	Percent Change	P-value*
Apolipoprotein B :							
Placebo	74	157.6	157.3	-0.4	0.8588	0.5	0.7942
CSV 3.0 g	79	159.4	146.7	-12.7	<0.0001	-7.6	<0.0001
CSV 3.8 g	80	161.9	142.5	-19.4	<0.0001	-11.9	<0.0001
CSV 4.5 g	75	155.2	136.1	-19.1	<0.001	-12.1	<0.0001

* P-value based on paired t-test from Day 0 to Day 168

Comments:

The mean change and percent change in apolipoprotein B from Day 0 to Day 168 were statistically significant in each of the Colesevelam-treated groups. This is expected as LDL-C decreased significantly in all the Colesevelam-treated groups as shown in Table III-3& 4.

e. The mean change and percent change in lipoprotein Lp(a) and apolipoprotein A-1 were not statistically significantly different between the placebo- and Colesevelam-treated groups.

V. Reviewer's Evaluation:

A. Primary Efficacy: 6 months of Colesevelam monotherapy resulted in statistically significant lowering of LDL-C in all Colesevelam-treated groups compared to placebo. However, LDL-C reductions >15% were obtained only at doses of 3.8 g and 4.5 g per day.

B. Secondary Efficacy: Statistically significant reductions in total-C were present in all Colesevelam-treated groups compared to placebo. The percent change from baseline to endpoint in total-C was -9.8% for the highest dose of 4.5 g. The clinical significance of these decrease is unknown. Small, statistically significant increases in HDL-C from baseline but not from placebo in all the CSV-treated groups were also demonstrated. The clinical significance of these increases is unknown. There were similar small increases in TG from baseline but not from placebo in all the CSV-treated groups. Again the clinical significance of these increases is unknown.

C. Safety:

As reviewed in the preceding pages (pp.11-14), there was no significant difference between the placebo-treated group and the colesevelam-treated groups in number of patients experiencing Serious Adverse Events. There were no clinically significant changes in liver function tests, in hematology parameters, in fat-soluble vitamins and coagulation parameters.

PROTOCOL GTC-48-302: This was a pivotal Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-design study.

I. Objectives:

The primary objective of this study was to determine the efficacy and safety of once a day versus a split dosing regimen of Colesevelam in reducing serum LDL-C levels in patients with primary hyperchole4sterolemia.

A. Patient Selection:

1. **Inclusion Criteria:** Similar to that of Protocol GTC-48-301 except: LDL-C level at Visit 2 >145 mg/dL but <250 and a TG <300 mg/dL
2. **Exclusion Criteria:** Identical to Protocol GTC-48-301.

II. Study Design and Procedures:

Following screening, 177 patients with primary hypercholesterolemia entered the diet period. After a minimum 6 weeks diet period patients meeting the entrance criteria were enrolled into one the following dosage groups:

1. Single daily dose Colesevelam 3.8 g: 10 capsules of Colesevelam with the early.meal (the AM group).
2. Placebo : 10 capsules of Placebo daily with the early meal
3. Single daily dose of Colesevelam 3.8 g: 10 capsules of Colesevelam with the late meal (the PM group).
4. Placebo: 10 capsules of placebo with the late meal.
5. Divided daily dose: 5 capsules Colesevelam BID with the early and late meals (the BID group).
6. Placebo: 5 capsules of placebo BID with the early and late meals.

The detailed study procedures are shown below:

Table II-1: Flow Chart

Study Period	Screening	Diet			Treatment		
Visit # Days	1	2 -21±3	3 -7±3	4 Day 0	5 14±3	6 28±3	7 42±3
Med./medication history.	*						
PE/vital Signs		*					*
Chem. Profile CBC	*						*
PT, PTT				*			
Serum HCG	*			*			
Fasting Lipid profile	*	*	*	*	*	*	*
TSH/T4	*						
Diet information.	*	*	*	*	*	*	*
Dispense Drugs				*	*	*	*
Adverse Events		*	*	*	*	*	*
Concomitant Medications	*	*	*	*	*	*	*

II A. Patient Accounting: Of the 177 patients screened, 79 patients discontinued prior to randomization. The primary reason for discontinuation was non-qualification for entry (88.6%). Therefore, a total of 98 patients were randomized into the treatment period. 90 patients completed the study. Reasons for premature discontinuation included adverse event (5.1%), withdrawal of consent (1.0%), death (1.0%), and other (1.0%).

Table II-2: Summary of Analyzed Populations—All Randomized Patients

	Placebo	CSV AM	CSV PM	CSV BID	Total
Reason for exclusion	N	N	N	N	N
Safety Population	23	27	24	24	98
No post-baseline valid lipid evaluation	1	2	1	0	4
ITT Population	22	25	23	24	94
Didn't complete Day 42	1	0	1	2	4
Compliance <80%	3	2	3	5	13
Evaluable Population	18	23	19	17	77

Comments:

1. The Safety population was defined as the randomized patients who took at least one dose of the study medication.
2. The ITT population included those patients who had at least one valid (12-hour fasting state and medication taken within 48 hours) post-baseline lipid evaluation.

3. The Evaluable population was defined as those patients who completed the study at Day 42, and were at least 80% compliant to the study medication.

II. B: Patient Characteristics: Demographic and other characteristics:

Table II-3. Selected Patient Demographics at Baseline, Intent-to-Treat Population

Variable	Placebo N=22	CCV AM N=25	CSV PM N=23	CSV BID N=24	Total N=94
Gender					
Male n(%)	12 (54.5)	11(44.0)	12(52.2)	11(45.8)	46(48.9)
Female n(%)	10(45.5)	14(56.0)	11(47.8)	13(54.2)	48(51.1)
Female menopausal and hormone supplement status					
Pre-meno/Post with hormone	4(40.0)	7(50.0)	4(36.4)	5(38.5)	20(41.7)
Post w/o hormone	6(60.0)	7(50.0)	7(63.6)	8(81.5)	28(58.3)
Body Mass Index (kg/m^2)					
Mean	26.1	25.5	26.5	26.4	26.1
Baseline LDL-C (mg/dL)					
<160 n(%)	7 (31.8)	9(36.0)	11(47.8)	10(41.7)	37(39.4)
160-190 n(%)	13(59.1)	12(48.0)	8(34.8)	7(29.2)	40(42.6)
>190 n(%)	2(9.1)	4(16.0)	4(17.4)	7(29.2)	17(18.1)

Pre-meno/post w/hormone=pre-& post menopausal females with hormone supplement.
Post w/o hormone=post menopausal females without hormone supplement.

Comments:

The sponsor performed ANOVA for continuous variables and Chi Square test for categorical variables. There were no statistical differences across treatment groups in the variables listed

III. Results:

A. Safety:

1. Death: There was one death in this study due to cardiac arrhythmia.
2. Serious Clinical Adverse Events: There were three serious adverse events reported in three patients during the study, two of which occurred during the diet phase of the study. Three other patients withdrew from the study also due to adverse events as shown below:

Table III-1: Patients Prematurely Discontinuing Treatment Due to Adverse Events:

Patient ID	Treatment Group	Primary Reason for Discontinuation	Exposure (Days)
001.003	CSV AM	Pain, constipation & dizziness	8
003.003	CSV PM	Sudden death d/t cardiac arrhythmia	4
003.025	CSV AM	Nausea & vomiting	7
003.032	Placebo	Abdominal pain, diarrhea, & flatulence	14
004.002	Placebo	Diarrhea	6
004.004	CSV BID	Anxiety	13

3. Laboratory Changes:
   a. There were statistically significant increases in mean alkaline phosphatase levels in all the CSV-treated groups. However, the increases were <2XULN) and no patient had >3XULN.
   b. Similarly, ALT abnormalities occurred in 8.3%--26.9% of the patients in the CSV treatment groups. A total of 13 patients had elevations. 12/13 had elevations <2X ULN, 1/13 had slightly >2XULN and no patient had >3XULN.
   c. There were no statistically significant changes in mean hematology parameters. No patient had clinically significant changes.
   d. There was a statistically significant decrease in PT in the CG AM and CG PM groups. No patient had PT >1.2XULN/>20 seconds

B. Efficacy: The mean and median changes in LDL-C, total-C, HDL-C, and TG from baseline to the end of the treatment period were the efficacy parameters. These changes are shown in the following tables:

Table III-2A: Mean and Median Percent Change in LDL-C (mg/dL) from Baseline to Endpoint—ITT Population:

		Baseline		Endpoint		Percent Change		
Treatment	N	Mean	Median	Mean	Median	Mean	Median	P-value*
Placebo	22	169.3	167.0	173.5	169.0	2.8	2.9	0.2999
CSV AM	25	167.5	163.0	137.0	137.0	-17.6	-18.7	<0.0001
CSV PM	23	165.1	165.1	140.9	143.0	-14.6	-14.6	<0.0001
CSV BID	24	173.8	163.0	141.9	138.5	-17.9	-15.4	<0.0001

* P-values based on paired t-test from baseline to endpoint.

Table III-2-B: Percent Change in LDL-C from Baseline to Endpoint, Paired Comparisons Between Treatment Groups—ITT Population:

Treatment group	CSV AM	CSV PM	CSV BID
Placebo	<0.0001	<0.0001	<0.0001
CSV AM		0.3575	0.9268
CSV PM			0.3171

Statistical analysis using ANOVA. Table provided by the sponsor.
Comments:

1. The mean and median percent changes in LDL-C were statistically significant for all the active treatment groups.
2. The mean percent decrease in LDL-C for the 3 CSV-treatment groups were –17.6% (AM); -14.6% (PM); and –17.9% (BID). The overall mean percent LDL-C reduction was –16.7% .
3. A paired comparison of these mean changes across the three dosing regimens of Colesevelam did not show statistically significant difference in the reduction of LDL-C.
4. Similar non-significant difference across the dosing groups were present in Total-C, HDL-C and TG changes.

IV. Reviewer's Evaluation:

A. Safety: There was no statistically significant difference between treatment groups in number of patients experiencing any treatment-emergent adverse events. There were no clinically significant changes liver function tests, in fat-soluble vitamins and coagulation parameters.

B. Efficacy: For the LDL-C and Total-C, once per day dosing with breakfast or dinner resulted in similar reductions as BID dosing between meals. For HDL-C and TG all dosing groups showed small median increases and there were no statistically significant differences between the groups.

Protocol GTC-37-901: This was a dose titration extension study of Protocol GTC 48-301,(Patients from GTC-37-201, GTC-37-202 and GTC-37-203 were also recruited.)

I. Objectives:

The primary objectives of this study were to determine the long-term safety and efficacy of Colesevelam in patients with primary hyperchole4sterolemia.

II. Patient Selection:

A. Inclusion Criteria:

1 Men or women 18 years or older.
2. Completed a previous Colesevelam trial.